X-linked adrenoleukodystrophy

Description

X-linked adrenoleukodystrophy is a genetic disorder that mainly affects the nervous system and the adrenal glands, which are small glands located on top of each kidney. In this disorder, the fatty covering (myelin) that insulates nerves in the brain and spinal cord tends to deteriorate (a condition called demyelination). The loss of myelin reduces the ability of the nerves to relay information to the brain. In addition, damage to the outer layer of the adrenal glands (adrenal cortex) causes a shortage of certain hormones (adrenocortical insufficiency). Adrenocortical insufficiency may cause weakness, weight loss, skin changes, vomiting, and coma.

There are four distinct types of X-linked adrenoleukodystrophy: a childhood cerebral form, an adrenomyeloneuropathy type, an adrenal insufficiency only form, and a type called asymptomatic.

The childhood cerebral form of X-linked adrenoleukodystrophy typically occurs in boys because girls are rarely affected with this type. If not treated, affected boys experience learning and behavioral problems that usually begin between the ages of 4 and 10. Over time the symptoms can worsen, and these children may have difficulty reading, writing, understanding speech, and comprehending written material. Additional signs and symptoms of the cerebral form include aggressive behavior, vision problems, difficulty swallowing, poor coordination, and impaired adrenal gland function. The rate at which this disorder progresses is variable but can be extremely rapid, often leading to total disability within a few years. The life expectancy of individuals with this type depends on whether early diagnosis and treatment are available. Without treatment, individuals with the cerebral form of X-linked adrenoleukodystrophy usually survive only a few years after symptoms begin.

Signs and symptoms of the adrenomyeloneuropathy type appear between early adulthood and middle age. Affected individuals develop progressive stiffness and weakness in their legs (paraparesis), experience urinary and genital tract disorders, and often show changes in behavior and thinking ability. Most people with the adrenomyeloneuropathy type also have adrenocortical insufficiency. In some severely affected individuals, damage to the brain and nervous system can lead to early death.

People with X-linked adrenoleukodystrophy whose only symptom is adrenocortical insufficiency are said to have the adrenal insufficiency only form. In these individuals, adrenocortical insufficiency can begin anytime between childhood and adulthood.

However, most affected individuals develop the additional features of the adrenomyeloneuropathy type by the time they reach middle age. The life expectancy of individuals with this form depends on the severity of the signs and symptoms, but typically this is the mildest of the three types.

Children with the asymptomatic form do not appear to have any symptoms of the condition, but medical testing may show brain or biochemical abnormalities. Some individuals with the asymptomatic form may develop features of other types of X-linked adrenoleukodystrophy later in life.

Rarely, individuals with X-linked adrenoleukodystrophy develop multiple features of the disorder in adolescence or early adulthood. In addition to adrenocortical insufficiency, these individuals usually have psychiatric disorders and a loss of intellectual function (dementia). It is unclear whether these individuals have a distinct form of the condition or a variation of one of the previously described types.

For reasons that are unclear, different forms of X-linked adrenoleukodystrophy can be seen in affected individuals within the same family.

Frequency

The prevalence of X-linked adrenoleukodystrophy is 1 in 15,000 individuals worldwide. This condition occurs with a similar frequency in all populations.

Causes

Mutations in the *ABCD1* gene cause X-linked adrenoleukodystrophy. The *ABCD1* gene provides instructions for producing the adrenoleukodystrophy protein (ALDP), which is involved in transporting certain fat molecules called very long-chain fatty acids (VLCFAs) into peroxisomes. Peroxisomes are small sacs within cells that process many types of molecules, including VLCFAs.

ABCD1 gene mutations result in a shortage (deficiency) of ALDP. When this protein is lacking, the transport and subsequent breakdown of VLCFAs is disrupted, causing abnormally high levels of these fats in the body. The accumulation of VLCFAs may be toxic to the adrenal cortex and myelin. Research suggests that the accumulation of VLCFAs triggers an inflammatory response in the brain, which could lead to the breakdown of myelin. The destruction of these tissues leads to the signs and symptoms of X-linked adrenoleukodystrophy.

Learn more about the gene associated with X-linked adrenoleukodystrophy

- ABCD1

Inheritance

X-linked adrenoleukodystrophy is inherited in an X-linked pattern. A condition is

considered X-linked if the mutated gene that causes the disorder is located on the X chromosome, one of the two sex chromosomes in each cell. In males (who have only one X chromosome), one altered copy of the *ABCD1* gene in each cell is sufficient to cause X-linked adrenoleukodystrophy. Additionally, affected males pass the altered gene to all of their daughters but none of their sons.

Because females have two copies of the X chromosome, one altered copy of the *ABCD1* gene in each cell usually does not cause features of X-linked adrenoleukodystrophy that are as severe as those in affected males. Most females with one altered copy of the gene develop some health problems associated with this disorder. Additionally, affected females have a 50 percent chance of passing the altered gene to each of their children.

The signs and symptoms of X-linked adrenoleukodystrophy tend to appear at a later age in females than in males. Affected women usually develop features of the adrenomyeloneuropathy type.

Other Names for This Condition

- Melanodermic leukodystrophy
- Schilder disease
- Siemerling-Creutzfeldt disease
- X-ALD

Additional Information & Resources

Genetic Testing Information

- Genetic Testing Registry: Adrenoleukodystrophy (https://www.ncbi.nlm.nih.gov/gtr/conditions/C0162309/)

Genetic and Rare Diseases Information Center

- X-linked adrenoleukodystrophy (https://rarediseases.info.nih.gov/diseases/5758/x-linked-adrenoleukodystrophy)

Patient Support and Advocacy Resources

- Disease InfoSearch (https://www.diseaseinfosearch.org/)
- National Organization for Rare Disorders (NORD) (https://rarediseases.org/)

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov (https://clinicaltrials.gov/ct2/results?cond=%22x-linked+adrenoleu

kodystrophy%22)

Catalog of Genes and Diseases from OMIM

- ADRENOLEUKODYSTROPHY (https://omim.org/entry/300100)

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28Adrenoleukodystrophy%5BMAJR%5D%29+AND+%28X-linked+adrenoleukodystrophy%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

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